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Review Article

Oral Anti-Platelet Therapy for Acute Coronary Syndrome

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Abstract

In recent days, medical treatment of coronary artery disease, and more specifically acute coronary syndrome with and without revascularization, has seen significant improvement in outcomes driven by the discovery of newer $P2Y_{12}$ receptor antagnosists leading to more consistent inhibition of platelet function and fewer ischemic and/or thrombotic events. This review will address a thorough analysis of this medical breakthrough.

Keywords: Disease, coronary syndrome, revascularization, receptor, platelet function

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1. Introduction

Platelet function inhibition is the foundation of treatment of unstable coronary artery disease, as evident by the 2014 AHA/ACC guidelines for the management of patients with Non-ST Elevation MI (NSTEMI) and the 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, labeling the administration of dual anti-platelet therapy with the highest recommendation [1,2]. Despite the increasing number of anti-platelet agents available for clinical use, the irreversible inhibition of cyclooxygenase 1 (COX-1) enzyme and subsequent suppression of prostaglandin and thromboxane synthesis using aspirin has remained the cornerstone of anti-platelet therapy. In addition, other pathways of platelet activation can be effectively targeted, as seen in multiple clinical trials that have demonstrated superiority of a strategy involving the combination of an aspirin and an adenosine diphosphate (ADP)-receptor antagonist over aspirin monotherapy [3-5]. This review aims to explore and summarize recent clinical data behind the adoption of modern-era anti-platelet therapy in the treatment of unstable coronary artery disease.

2. Platelet activation and aggregation

Hemostasis involves complex interactions between platelets, vascular endothelial cells and clotting factors. Normal hemostasis is achieved by a balance between procoagulant and anticoagulant factors in a structurally intact vasculature. Intact vascular endothelial cells have the dual function of shielding platelets from the highly thrombogenic subendothelium, while secreted nitric oxide and prostacyclin promote cyclic AMP production within platelets thus preventing platelet activation and aggregation [6].

Platelets form the initial platform and mediate between the various components of the hemostatic response system, either in physiologic or pathological situations. The initial response to an activating stimulus is platelet adhesion to endothelium and subendothelium, followed by activation of platelet membrane receptors, translocation of further receptors to the platelet surface, release of granule content and recruitment of membrane phospholipids. In addition, activated platelet surfaces provide a platform for fibrin production, leading to the formation of a hemostatic plug. Platelets anchor to the damaged vascular wall initially through the binding of subendothelial Von Willebrand factor (vWF) to the GPIb receptor on platelet membrane and binding of the GPIa/IIa receptor to subendothelial collagen [7]. Parallel to platelet adhesion is platelet activation, which involves the release of ligands leading to further platelet recruitment, acceleration of platelet-associated fibrin formation and stabilization of the hemostatic plug. Following hemostatic plug formation, platelet aggregation ensues, with the central component in this process being the platelet membrane GPIIb/IIIa receptor. The GPIIb/IIIa receptor is the most abundant platelet membrane glycoprotein, with approximately 80,000 copies on the surface of an inactivated platelet, which increases by approximately 50% upon platelet activation [8,9]. GPIIb/IIIa receptor binds to vWF multimers and/or fibrinogen secreted from activated platelet alpha granules, resulting in cross-linking of platelets and subsequent platelet aggregation.

It is important to mention that one of the reasons behind the difference in treatment between thrombotic arterial and venous disease is the difference in relative importance of platelet involvement in such processes. In the highly pressurized arterial circulation, platelets form the initial plug in order to rapidly contain blood loss, and subsequently provide the milieu for fibrin formation and achievement of hemostasis (and hence anti-platelet agents are effective in treating arterial thrombotic events), whereas in the low pressure venous circulation activation of the coagulation cascade and fibrin formation plays the decisive role in containment of blood loss (and hence anti-coagulants are effective in treating venous thrombotic disease) [10].

3. Treatments and Discussions

Aspirin

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) that irreversibly inhibits COX-1 enzyme and suppresses synthesis of prostaglandins and thromboxane A2. Aspirin began to emerge as a major therapy for acute coronary syndrome (ACS) in the 1980s, where early clinical trials showed that aspirin reduced the incidence of recurrent ischemic events and death in ACS [11-16]. The Veterans Administration (VA) Cooperation Study [11], initiated in 1974 and published in 1983, was a multicenter, double-blind, placebo-controlled trial examining the benefits of 324mg of aspirin for 12 weeks versus placebo in 1266 men with unstable angina. Patients receiving aspirin had a statistically

significant lower incidence of fatal or nonfatal acute myocardial infarction (7.8% vs. 3.5%, *P* value < 0.01) and a non-statistically significant trend towards lower mortality (3.3% vs. 1.6%, *P* value = 0.05) with no increase in bleeding complications. The VA Cooperation Study was the first trial to show a statistically significant benefit (prior trials only showed a trend towards lower events without reaching statistical significance) [12-16]. These findings where further substantiated in the Second International Study of Infarct Survival trial (ISIS-2) that randomized 17,187 acute myocardial infarction patients into treatment with (1) IV Streptokinase, (2) one month of 160mg daily of aspirin, (3) both medications or (4) neither treatment. Patients receiving aspirin, compared with placebo, had a significantly lower incidence of vascular death (9.4% vs. 11.8%, *P* value < 0.01), reinfarction (1.0% vs. 2.0%, *P* value < 0.01) and stroke (0.3% vs. 0.6%, *P* value < 0.01) [17]. Similar findings were subsequently duplicated in large trials and meta-analyses, with the Antithrombotic Trialists' Collaboration meta-analysis pooling 287 studies and analyzing outcomes in high-risk patients (patients with risk factors or known vascular disease), finding that aspirin use in a dose of at least 150mg daily in the acute phase and 75-150mg daily long-term was protective from major occlusive vascular events [18].

An important clinical aspect regarding the use of aspirin has been regarding the optimal maintenance dose of aspirin. Historical studies had examined significantly higher doses of aspirin, such as 900mg [15] or 1gm [16] daily, in patients with coronary disease. Subsequent trials and analyses showed that optimal COX-1 inhibition (and subsequent reduction in platelet activity) could be achieved with the lower dose of 325mg, thereby minimizing side effects [11,19,20]. In addition, CURRENT OASIS 7 was a randomized clinical trial in 25,086 ACS (both NSTEMI and STEMI) patients undergoing coronary angiography and examining the effect of double-dose clopidogrel load or standard-dose clopidogrel and either higher-dose aspirin (300 to 325mg daily) or lower-dose aspirin (75 to 100 mg daily), while TRANSLATE-ACS was a non-randomized, prospective trial of 10,213 ACS patients undergoing percutaneous coronary intervention and discharged on a daily aspirin dose of either 81mg or 325mg. Both trials showed similar cardiovascular outcomes between lose dose (75 to 100mg daily) and higher dose aspirin patients (325mg daily) with higher incidence of bleeding events in patients taking 325mg of aspirin [21,22]. The leading theory behind the advantage of using lower dose aspirin lies in the fact that aspirin not only inhibits platelet cyclooxygenase (which in turn prevents the production of thromboxane A_2 that is an extremely potent vasoconstrictor and stimulus for platelet aggregation) but it also inhibits arterial wall cyclooxygenase (which produces prostacyclin and has the opposite effects of thromboxane A2), which tends to be less susceptible to the actions of aspirin than platelet cyclooxygenase [19]. This is supported by the observation that a single dose of 300mg of aspirin increases cutaneous bleeding whereas a larger dose of 3.9gm does not [20].

Aspirin and Warfarin vs. Aspirin

Despite the use of aspirin and other potent anti-platelet agents in treating patients with acute coronary syndrome, there persists a risk of recurrent cardiovascular events that includes a 2.0-2.2% risk of in-hospital mortality [23], 2.4% risk of in-hospital recurrent MI, 0.5% risk of in-hospital stroke and a 10% risk of in-hospital heart failure or shock [24]. Furthermore, there has been evidence pointing towards activation of the coagulation cascade beyond that of the acute event [25]. As a result, the potential added benefit of anti-coagulant therapy, primarily using a Vitamin K antagonist such as warfarin, in patients with acute coronary syndrome has been extensively investigated.

Trials evaluating chronic administration of anti-coagulant and anti-platelet therapy in acute coronary syndrome patients, without other indications for chronic anti-coagulation, have yielded similar conclusions: there is a significant reduction in cardiovascular events (especially when the INR is maintained between 2 and 3) with an offset of benefit due to an increased risk of bleeding [26]. The Coumadin Aspirin Reinfarction Study (CARS, 1997) compared outcomes in 8803 patients with previous myocardial infarction who either received 160mg of aspirin, 3mg of warfarin with 80mg aspirin, or 1mg warfarin with 80mg aspirin and found no benefit in cardiovascular outcomes with the addition of low dose warfarin (either 1mg or 3mg) to low dose aspirin (80mg) compared with 160mg aspirin monotherapy [27]. The Organization to Assess Strategies for Ischemic Syndromes trial (OASIS-2, 2001), which enrolled 3712 patients with unstable angina on aspirin, found no benefit of adding warfarin in the overall population but suggested benefit with lower cardiovascular events in more compliant patients [28]. The Combination Hemotherapy and Mortality

Prevention Study (Champ, 2002) paralleled the findings of CARS and OASIS-2 in finding no benefit of adding warfarin (at a mean INR of 1.8) to low dose aspirin in 5059 patients enrolled within 2 weeks of a myocardial infarction and followed for a median of 2.7 years [29]. On the other hand, the Warfarin, Aspirin, Reinfarction Study (WARIS II, 2002) enrolled 3630 patients post myocardial infarction and showed a statistically significant reduced incidence of death, nonfatal reinfarction or thromboembolic cerebral stroke with more aggressive warfarin therapy, but was also associated with increased risk of bleeding (mean INR was 2.8 in warfarin monotherapy and 2.2 in patients receiving aspirin and warfarin) [30]. Finally, the low-dose warfarin and aspirin trial (LoWASA, 2004) confirmed the lack of benefit from the addition of warfarin to aspirin in 3300 post MI patients followed up for a median of 5 years [31]. These findings were further corroborated in large meta-analyses stratifying outcomes by INR levels and confirming the trend of less cardiovascular events with higher INRs but with greater risk of bleeding [32,33].

There has been considerable interest in the use of novel oral anticoagulant agents (that are non-vitamin K antagonists) given the predictable pharmacokinetic and pharmacodynamics profiles. It is noteworthy to briefly mention the results of the ATLAS ACS 2–TIMI 51 randomized trial, which investigated the benefit of rivaroxaban in 15,526 patients with recent acute coronary syndrome who were already on dual anti-platelet therapy, and found a significant benefit with reduced cardiovascular events but with increased risk of major bleeding and intracranial hemorrhage [34].

Clopidogrel

Clopidogrel is an oral thienopyridine pro-drug that is rapidly absorbed by the gastrointestinal tract and undergoes extensive hepatic metabolism into either an (1) inactive carboxylic acid derivative via esterase-mediated hydrolysis, or an (2) active thiol metabolite via CYP450-mediated oxidation. Clopidogrel is an irreversible antagonist of the ADP-activated $P2Y_{12}$ receptor, which blocks activation of the GPIIb/IIIa receptor complex and leads to reduction in platelet aggregation [35]. Clopidogrel administration (loading dose of 300mg or 600mg followed by a maintenance dose of 75mg) has been labeled as a Class I recommendation by the 2014 AHA/ACC guidelines as an addition to aspirin in acute coronary syndrome patients without contraindications who are treated with either an early invasive or an ischemia-driven approach [1]. The benefit of adding clopidogrel has been unequivocally demonstrated in randomized trials enrolling patients with acute coronary syndrome as well as patients undergoing percutaneous coronary intervention.

CURE, COMMIT and CLARITY-TIMI 28

Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) was a randomized, multicenter trial of 12,562 unstable angina patients randomized to clopidogrel or placebo in addition to aspirin [3]. The CURE trial was planned based on the findings of the CAPRIE trial, which showed that clopidogrel was more efficacious in preventing cardiovascular events over a mean follow-up period of 1.9 years in a population of patients with symptomatic atherosclerotic vascular disease than aspirin [36]. In the CURE trial, patients were randomized within 24 hours of symptom onset, with the primary outcome (a composite of cardiovascular death, non-fatal MI or stroke) occurring in 9.3% in the clopidogrel arm versus 11.4% in the placebo arm ($P < 0.01$). However, there was more major bleeding in the clopidogrel arm (3.7% vs. 2.7%, $P < 0.01$) with no increase in life-threatening bleeding (2.2% vs. 1.8%, $P = 0.13$). The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) trial focused on 45,852 acute myocardial infarction patients, and found that the addition of clopidogrel compared to placebo significantly reduced the composite incidence of death, reinfarction or stroke (9.2% vs. 10.1%, $P < 0.01$) without an increase in bleeding events (0.58% vs. 0.55%, $P = 0.59$) [4]. In addition, patients younger than 75 years of age suffering from an ST-Elevation MI receiving aspirin, clopidogrel and fibrinolytic therapy in the CLARITY–TIMI 28 trial had improved infarct-related artery patency with lower ischemic complications without an increase in bleeding complications [5].

CLASSICS, PCI-CURE and CREDO

Similar findings of the beneficial effect of clopidogrel in addition to aspirin were observed in patients undergoing percutaneous intervention. The combination of aspirin and ticlodipine had been the standard of treatment in patients undergoing coronary stenting for the prevention of in-stent thrombosis. However, given the emerging cardiovascular benefits of clopidogrel coupled with a better safety profile compared to ticlodipine, the

CLASSICS trial was devised examining the difference in procedural and 30-day outcomes in patients undergoing percutaneous coronary intervention and receiving aspirin and clopidogrel or aspirin and ticlodipine [37]. CLASSICS showed equivalent efficacy between clopidogrel and ticlodipine in terms of procedural success, hospital length of stay or thrombotic events, and 30-day major cardiovascular event (MACE) rate. Furthermore, the PCI-CURE trial showed that pre-treatment with clopidogrel followed by long-term therapy (a mean of 8 months) was beneficial in reducing cardiovascular events (4.5% vs. 6.4% in placebo, *P* value = 0.03). Similar findings were reported in the CREDO trial, where long-term clopidogrel therapy was continued for 1 year [38].

Clopidogrel and Proton Pump Inhibitors

There has been a lot of debate regarding the effect of proton pump inhibitors (PPIs) on the metabolism and activation of clopidogrel through the hepatic cytochrome P450 system. Patients with coronary artery disease receiving dual anti-platelet therapy following coronary stenting are commonly treated with PPIs to reduce the risk of gastrointestinal bleeding. Recent pharmacological studies have shown that PPIs reduce clopidogrel-mediated inhibition of platelet aggregation through inhibition of the CYP P450 enzyme [39,40]. Yet, clinical trials have yielded conflicting data about the short-term mortality effect of the concomitant usage of PPIs and dual anti-platelet therapy. Some studies have shown that PPI administration with aspirin and clopidogrel increases short-term cardiovascular events [41,42], whereas others have shown no significant difference [43]. Overall, the effect of PPI on platelet aggregation, in patients on clopidogrel, is small and not clinically significant, as corroborated in large randomized trials and subsequent meta-analyses [44,45]. As a result, the 2016 ACC/AHA focused update recommends the use of a PPI with DAPT in patients who are assessed to be at an increased risk of bleeding (Class IIa indication) [46].

Prasugrel

Prasugrel belongs to the same thienopyridine class as clopidogrel, acts by irreversible blockade of the $P2Y_{12}$ receptor. Prasugrel has more favorable pharmacokinetics over clopidogrel, with more rapid onset of action, higher potency and more consistent inhibition of platelet aggregation as prasugrel is more efficiently metabolized by hepatic esterases and is less dependent on the cytochrome P450 system for conversion into its active metabolite [47]. The development of prasugrel occurred in an attempt to overcome the limitations of clopidogrel use: delayed onset of action, variable and inconsistent platelet function inhibition and clopidogrel resistance leading to adverse cardiovascular outcomes [48]. Prasugrel has a class I indication to be used as a loading dose of 60mg followed by a maintenance dose of 10mg daily in ACS patients undergoing percutaneous coronary intervention with stent placement [1].

TRITON-TIMI 38, TRILOGY ACS & ACCOAST

Prasugrel approval for use was largely based off the findings of the Trial to assess Improvement in Therapeutic outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis In myocardial Infarction 38 (TRITON–TIMI 38) trial, which was a double-blind, randomized controlled trial that enrolled 13,608 acute coronary syndrome patients who were scheduled to undergo percutaneous coronary intervention, and were randomized to receive clopidogrel (loading dose of 300mg followed by maintenance of 75mg daily) or prasugrel (loading dose of 60mg followed by maintenance of 10mg daily) in addition to aspirin therapy [49]. The primary efficacy endpoint, which was a composite of cardiovascular death, nonfatal MI or stroke, was significantly lower in the prasugrel arm compared to clopidogrel (9.9% vs. 12.1%, *P* value < 0.01). There was also an advantage to prasugrel in terms of lower incidence of MI, urgent target vessel revascularization and stent thrombosis. In terms of safety endpoints, patients receiving prasugrel had a higher incidence of life-threatening (1.4% vs. 0.9%, *P* = 0.01) and fatal bleeding (0.4% vs. 0.1%, *P* < 0.01). Subgroup analysis revealed that patients with previous stroke or transient ischemic attack (TIA) had net harm from prasugrel, while patients older than 75 or weighing less than 60Kg had no net benefit.

Interestingly, prasugrel had no benefit in terms of reduction in cardiovascular death or events in acute coronary syndrome patients managed without revascularization, as seen in The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial which enrolled 7243 patients and had a median follow up of 17 months [50]. Unlike clopidogrel, the ACCOAST trial showed no benefit of pre-treatment with prasugrel in 4033 acute coronary syndrome undergoing angiography compared to treatment at the time of

intervention, with an increased risk of major bleeding complication [51].

Ticagrelor

Unlike clopidogrel or prasugrel, ticagrelor is a cyclo-pentyltriazolo-pyrimidine that directly and reversibly inhibits the $P2Y_{12}$ receptor [52]. Similar to clopidogrel, it carries a class I indication for use in acute coronary syndrome patients undergoing an early invasive or ischemia-guided strategy, and has a class IIa indication for the use in preference to clopidogrel [1]. The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial investigated outcomes in 18,624 acute coronary syndrome patients receiving clopidogrel versus ticagrelor in addition to aspirin [53]. The incidence of the primary end point, a composite of vascular death, MI or stroke, was significantly lower in the ticagrelor arm compared to clopidogrel (9.8% vs. 11.7%, $P < 0.01$), with a significant reduction in the separate incidence of death from any cause, vascular death as well as myocardial infarction. There was no significant difference between clopidogrel and ticagrelor in terms of rates of major bleeding, but patients receiving ticagrelor had higher incidence of major bleeding not related to coronary artery bypass grafting (4.5% vs. 3.8%, $P = 0.03$).

4. Conclusion

In conclusion, medical treatment of coronary artery disease, and more specifically acute coronary syndrome with and without revascularization, has seen significant improvement in outcomes driven by the discovery of newer $P2Y_{12}$ receptor antagnosists leading to more consistent inhibition of platelet function and fewer ischemic and/or thrombotic events.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this article.

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